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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,344	12/04/2001	Loren J. Miraglia	ISPH-0622	8099

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EXAMINER
GIBBS, TERRA C

ART UNIT	PAPER NUMBER
1635	8

DATE MAILED: 01/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,344	MIRAGLIA ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-50* is/are pending in the application.

4a) Of the above claim(s) *12-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to the Election filed 11/5/02, in Paper No. 7.

Claim 43 has been canceled. Claims 1, 2, 3 and 5-50 are pending in the instant application.

Claims 12-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

Claims 1-3 and 5-11 have been examined as they read on the elected subject matter.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-3 and 5-11) in Paper No. 7 is acknowledged. The traversal is on the ground(s) that all of the claims are related to the single concept of modulating the expression of human mdm2. Further, Applicant argues that a search of literature relating to human mdm2 would clearly reveal art relating to all of the claims, and therefore would not place an undue burden on the examiner. This is not found persuasive because, as argued in the restriction requirement (Paper No. 6), the compounds of Groups I-II and the compound of Group V are drawn to chemically and structurally distinct compounds. Further argued, the compounds of Groups I and II target distinct regions of human mdm2 and are therefore distinct. Further, the compounds of Groups I and II may be used in other methods than those described in Groups III and IV. Therefore, a search for the compound of Group I will not encompass all of the art relevant to the compound of Group II. Also, a search of the compound

of Groups I-II will not encompass all of the art relevant to the compound of Group V. Finally, a search for the compounds of Groups I, II and V will not encompass all of the art relevant to the methods of Groups III and IV. With regard to the relationship of the claims as product, process of making and process of using, the argument is not persuasive because restriction is proper regardless of whether the claims are related as product and process of making or product, process of making and process of using. Where claims are drawn to a product, process of making and process of using, restriction may be required where the process of making and product made are distinct according to the guidelines set forth in MPEP 806.05(f) (see MPEP 806.05(i)), as was demonstrated for the product and process of using of the instant application.

Applicant's election of SEQ ID NO:1 with traverse in Paper No. 7 is acknowledged. The traversal is on the ground(s) that all of the identified antisense sequences recited share the ability to modulate a common structure, namely human mdm2 and are therefore not patentably distinct. This is not found persuasive because, as argued in the restriction requirement (Paper No. 6), pursuant to 35 U.S.C. 121 and 37 C.F.R. 1.141, up to 10 independent and distinct nucleotide sequences will be examined in a single application (see MPEP 803.04 and 2434). Furthermore, as argued in the restriction requirement, each antisense sequence has a unique nucleotide sequence, each antisense sequence targets a different and specific region of human mdm2, and each antisense, upon binding to human mdm2, functionally modulates (increases or decreases) the expression of the gene to a varying degree (per applicant's Table 12 in the specification). These independent antisense sequences are therefore distinct. Further, as stated in the restriction requirement, a search of more than one (1) of the antisense sequences claimed presents an undue

burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed antisense sequences.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 9 relies on claim 8 and recites the limitation "2'-O-methoxyethyl modified cytidine residue". There is insufficient antecedent basis for this limitation in the claim since claim 8 does not recite "2'-O-methoxyethyl modified cytidine residue".

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 5 recites "S-mdm2 transcript". There is insufficient antecedent basis for this limitation in the claim. Claim 5 has not been further treated on the merits.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3 and 6-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,238,921 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the issued US Patent claims several species of antisense oligonucleotides targeting human mdm2 and the instant application claims a broad genus of antisense oligonucleotides targeting human mdm-2 which encompasses the species of antisense claimed in the issued Patent. The species of antisense oligonucleotides recited in the claims of the issued Patent render obvious the genus of antisense oligonucleotides recited in the instant application claims because as the MPEP § 2131.02 states, "A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus." The species in that case will anticipate the genus. *In re Slayter*, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960).

Claims 1-3 and 6-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,184,212 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the issued US Patent recite several species of antisense oligonucleotides targeting human mdm2 and the instant application claims a broad genus of antisense oligonucleotides targeting human mdm-2 which encompasses the species of antisense claimed in

the issued Patent. Additionally, the claims of the issued patent similarly recite pharmaceutical compositions and oligonucleotide modifications recited in the instant claims. The species of antisense oligonucleotides recited in the claims of the issued Patent render obvious the genus of antisense oligonucleotides recited in the claims of the instant invention for the reasons given above and those reasons discussed in the above rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 3 are rejected under 35 U.S.C. 102(a) as being anticipated by Chen et al. (Proceedings of the National Academy of Science, 1998 Vol. 95:195-200).

Claims 1, 2 and 3 are drawn to an antisense compound 8 to 30 nucleobases in length targeted to the 5' untranslated region, coding region, intron:exon junction, intron region, exon region, translation termination codon region or 3' untranslated region of a nucleic acid molecule encoding human mdm2 (SEQ ID NO:1), wherein the antisense compound modulates the expression of mdm2; wherein the antisense compound inhibits the expression of human mdm2; wherein the antisense compound is an antisense oligonucleotide.

Chen et al. disclose a human mdm2 antisense oligonucleotide, 20 nucleobases in length targeted to the coding region of mdm2 (see page 195, last column). Chen et al. further disclose

inhibition of mdm2 expression by antisense oligonucleotides targeted to the coding region of human mdm2 (see Figures 1A and 1B).

Claims 1, 2 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Teoh et al. (Blood, 1997 vol. 5:1982-1992).

Teoh et al. disclose two human mdm2 antisense oligonucleotides, 15 and 20 nucleobases in length targeted to the translation initiation start codon of the mdm2 coding region of mdm2 (see page 1983, last paragraph). Teoh et al. further disclose inhibition of mdm2 expression by antisense oligonucleotides targeted to the coding region of human mdm2 (see Figure 2).

Claims 1, 2 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Kondo et al. (Oncogene, 1995 Vol. 10:2001-2006).

Kondo et al. disclose a human mdm2 antisense oligonucleotide, 20 nucleobases in length targeted to the translation initiation start codon of the mdm2 coding region of mdm2 (see page 2005, last paragraph). Kondo et al. further disclose inhibition of mdm2 expression by antisense oligonucleotides targeted to the coding region of human mdm2 in tumor cells (see Figure 3A).

Claims 1, 2 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Kondo et al. (British Journal of Cancer, 1996 Vol. 74:1263-1268).

Kondo et al. disclose a human mdm2 antisense oligonucleotide, 20 nucleobases in length targeted to the translation initiation start codon of the mdm2 coding region of mdm2 (see page

1264, second column). Kondo et al. further disclose inhibition of mdm2 expression by antisense oligonucleotides targeted to the coding region of human mdm2 in tumor cells (see Figure 5).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 6-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burrell et al. (WO 93/20238) in view of Branch (TIBS, February 1998 Vol. 23, pages 45-50) and Monia et al [U.S. Patent No. 5,872,242].

Claims 1-3 and 6-9 are drawn an antisense compound 8 to 30 nucleobases in length targeted to the 5' untranslated region, coding region, intron:exon junction, intron region, exon region, translation termination codon region or 3' untranslated region of a nucleic acid molecule encoding human mdm2 (SEQ ID NO:1), wherein the antisense compound modulates the

expression of mdm2; wherein the antisense compound inhibits the expression of human mdm2; wherein the antisense compound contains at least one phosphorothioate intersugar linkage; wherein the antisense compound contains at least one 2'-O-methoxyethyl sugar modification; wherein the antisense compound contains at least one 5-methyl cytidine. Claims 10 and 11 are drawn to a composition comprising an antisense compound 8 to 30 nucleobases in length targeted to the 5' untranslated region, coding region, intron:exon junction, intron region, exon region, translation termination codon region or 3' untranslated region of a nucleic acid molecule encoding human mdm2 (SEQ ID NO:1), wherein the antisense compound modulates the expression of mdm2 and a pharmaceutically acceptable carrier or diluent, further comprising a lipid or liposome.

Burrell et al. discloses the entire antisense transcript of MDM2 and further discloses that antisense oligonucleotides targeted to unprocessed pre-mRNA or processed mRNA encoding MDM2 can be used to inhibit translation of MDM2 (p. 10). Burrell et al. also teach that the mdm2 gene functions in tumorigenesis, and that over expression of mdm2 causes cells to escape from p-53 regulated growth (p. 4). This reference goes on to teach that identifying means to inhibit the expression of mdm2 would have great therapeutic benefits (p. 10). However, Burrell et al. does not teach antisense oligonucleotides targeting the 5' untranslated region, coding region, intron:exon junction, intron region, exon region, translation termination codon region or 3' untranslated region of a nucleic acid molecule encoding human mdm2 (SEQ ID NO:1), wherein said antisense oligonucleotide comprises 8 to 30 nucleobases or comprising the modifications of antisense oligonucleotides according to the present invention.

Branch teach that in order to maximize target site specificity the length of antisense oligonucleotides should be 17 base pairs or longer, since sequences of 17 base pairs or more would have a high probability of occurring only once in the haploid human genome. However, increasing the length of the oligonucleotide beyond this minimum would likely stabilize non-specific binding to mismatch sequences (p. 47, para. 5-6).

Monia et al. describe methods for the modulation of expression of the human ras oncogene in a cell comprising the administration of modified antisense oligonucleotides. In a preferred embodiment of the Monia et al. reference, the oligonucleotide is targeted to a translation initiation site (AUG codon) or sequences in the coding region, 5' untranslated region or 3'-untranslated region of the targeted mRNA. By targeting all of these regions of the mRNA, these antisense oligonucleotides are intended to interfere with all vital functions of the target mRNA such as translocation of the RNA to the site for protein translation, actual translation of protein from the RNA, splicing or maturation of the RNA and possibly even independent catalytic activity which may be engaged in by the RNA (col. 6, lines 10-32).

The oligonucleotides of Monia et al. preferably are chimeric oligonucleotides that contain two or more chemically distinct regions, each made up of at least one nucleotide. These oligonucleotides typically contain at least one region of modified nucleotides that confers one or more beneficial properties (such as, for example, increased nuclease resistance, increased uptake into cells, increased binding affinity for the RNA target) and a region that is a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids (col. 6, lines 49-67). The modified antisense oligonucleotides used in the method of Monia et al. may comprise phosphorothioate internucleoside modifications, a 5-methylcytosine modifed nucleobase, and

may further comprise 2'-methoxyethoxy sugar modifications (col. 7-8). Monia et al. also disclosed pharmaceutical compositions comprising the oligonucleotides of this invention and a pharmaceutically acceptable salt, such as the cationic lipid formulation DMRIE:DOPE (col. 18, lines 46-47). The antisense oligonucleotide modifications disclosed by Monia et al. have been shown to increase both binding affinity of the oligonucleotide for its target and nuclease resistance of the oligonucleotide (col. 6, lines 45-58).

It would have been obvious to one of ordinary skill in the art to modify the teachings of Burell et al. to design antisense oligonucleotides of at least 17 nucleobases in length (Branch), modifying those antisense oligonucleotides with phosphorothioate linkages, 2'-methoxyethoxy modified sugar residues, and a 5'-methylcytosine modified nucleobase (Monia et al.), in order to maximize target site specificity (Branch), and increase hybridization efficiency as well as maintaining nuclease resistance of said antisense oligonucleotide (Monia et al.). Additionally, it would have been obvious to design antisense oligonucleotides targeting the 5' untranslated region, coding region, translation termination codon region or 3' untranslated region of an mRNA in order to interfere with all the vital functions of an mRNA according to Monia et al. Moreover, one of ordinary skill in the art would have been motivated to design antisense oligonucleotides of at least 17 nucleobases comprising the modifications taught by Monia et al. since oligonucleotides of this size possess a high target site specificity and increased cellular uptake in comparison to unmodified antisense oligonucleotides.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing over Burell et al. in view of Branch, and Monia et al.

Claims 1-3 and 6-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Chen et al. (Proceedings of the National Academy of Science, 1998 Vol. 95:195-200), Teoh et al. (Blood, 1997 vol. 5:1982-1992), Kondo et al. (Oncogene, 1995 Vol. 10:2001-2006), Kondo et al. (British Journal of Cancer, 1996 Vol. 74:1263-1268) in further view of Monia et al. [U.S. Patent No. 5,872,242].

Claims 1-3 and 6-11 are described above.

Chen et al., Teoh et al., Kondo et al. (1995) and Kondo et al. (1996) are relied upon as cited in the 102 rejection above.

Chen et al., Teoh et al., Kondo et al. (1995) and Kondo et al. (1996) do not teach antisense oligonucleotides targeting the 5' untranslated region, intron:exon junction, intron region, exon region, translation termination codon region or 3' untranslated region of a nucleic acid molecule encoding human mdm2 (SEQ ID NO:1), wherein said antisense oligonucleotide comprises 8 to 30 nucleobases or comprising the modifications of antisense oligonucleotides according to the present invention

Monia et al. describe methods for the modulation of expression of the human ras oncogene in a cell comprising the administration of modified antisense oligonucleotides. The oligonucleotides of Monia et al. preferably are chimeric oligonucleotides that contain two or more chemically distinct regions, each made up of at least one nucleotide. These oligonucleotides typically contain at least one region of modified nucleotides that confers one or more beneficial properties (such as, for example, increased nuclease resistance, increased uptake into cells, increased binding affinity for the RNA target) and a region that is a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids (col. 6, lines 49-67). The

modified antisense oligonucleotides used in the method of Monia et al. may comprise phosphorothioate internucleoside modifications, a 5-methylcytosine modifed nucleobase, and may further comprise 2'-methoxyethoxy sugar modifications (col. 7-8). Monia et al. also disclosed pharmaceutical compositions comprising the oligonucleotides of this invention and a pharmaceutically acceptable salt, such as the cationic lipid formulation DMRIE:DOPE (col. 18, lines 46-47). The antisense oligonucleotide modifications disclosed by Monia et al. have been shown to increase both binding affinity of the oligonucleotide for its target and nuclease resistance of the oligonucleotide (col. 6, lines 45-58).

It would have been obvious to one of ordinary skill in the art to modify the antisense compound of either Chen et al., Teoh et al., Kondo et al. (1995) or Kondo et al. (1996) by modifying said antisense compound with phosphorothioate linkages, 2'-methoxyethoxy modified sugar residues, and a 5'-methylcytosine modified nucleobase (Monia et al.), in order to increase hybridization efficiency as well as maintaining nuclease resistance of said antisense compound (Monia et al.). One of ordinary skill in the art would have been motivated to design antisense oligonucleotides comprising the modifications of Monia et al. since these modifications confer increased duplex stability with it's target nucleic acid and increased cellular uptake in comparison to unmodified antisense oligonucleotides.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing over either Chen et al., Teoh et al., Kondo et al. (1995) or Kondo et al. (1996) in view of Monia et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
January 6, 2003

SEAN McGARRY
PRIMARY EXAMINER